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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,792	07/28/2003	Jon A. Wolff	Mirus.040.01	5528

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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/628,792	WOLFF ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-8 and 12-30* is/are pending in the application.

4a) Of the above claim(s) *28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4, 6-8, 12-27, 29-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final rejection filed on April 21, 2008 is acknowledged. Claims 5 and 9-11 have been cancelled. Claim 28 remains withdrawn from further consideration as being drawn to nonelected species. Claims 1-2, 4, 6-8, 12-27 and 29-30 are examined on the merits in this office action.

Declaration under 37 C.F.R. 1.132

1. Declaration under 37 CFR 1.132 filed on April 21, 2008 is acknowledged and has been considered.

Withdrawn Rejection

2. Rejection of claims 1-2, 4-8, 12-27 and 29-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description is hereby withdrawn due to Applicant's arguments.

3. Rejection under 35 U.S.C. 102(e) is hereby withdrawn due to Applicant's amendment.

Maintained Rejection

35 U.S.C. 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-2, 4, 6-8, 12-27 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Twist et al (US Patent # 5633230).

6. The instant claims are drawn to a process for delivering a molecule, and the active steps of the process is inserting an injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue.

7. Twist et al teach the assessment of peptide distribution, in vivo. The distribution and localization of a ^{14}C-acetyl form of peptide AV9 was determined following administration by intravenous and sub-cutaneous injection dissolved in 10 ml PBS. The reference teaches that both i.v. and s.c. injection brought about rapid distribution of drug to tissues. The highest and most prolonged levels are attained in the liver, followed by the kidneys and spleen (see Example 4). Since the active steps of the process are disclosed in Twist patent '230, and the subsequent claims do not alter the active step of the process, Twist reference meets the limitations of claims 1-10, 12-27 and 29.

Response to Applicant's Arguments

8. Applicant argues that "Twist et al do not teach increasing vascular permeability, increasing extravascular fluid volume, swelling of the target tissue, or extravasation of the molecule via the increased vascular permeability. Twist et al does not provide a sufficient volume to cause a transient increase vascular permeability or increased extravascular fluid volume within a target tissue."

9. Applicant's arguments have been fully considered but have not been found persuasive because Twist et al teach the administration of protein or

peptide to the target tissues (liver, kidneys and spleen). The active steps of the process are disclosed in the Twist reference, and the subsequent claims do not alter the active steps of the process. The only active step recited in the base claim is "inserting an injection solution containing protein or peptide into the lumen of an efferent or afferent vessel of the target tissue." The instant claims do not recite the volume injected, or the pressure applied. Therefore, the amount of injection administered in the Twist reference would cause a transient increased vascular permeability in the target tissue, since the injection solution taught in the Twist reference is hypertonic. Hypertonic injection solutions would inherently increase the permeability. In the declaration under 37 C.F.R. 1.132, Applicant argues that the “injection volume of 400 μL injected by Twist reference into the tail vein of a mouse resulted in no measurable increase in intravascular pressure in the Inferior Vena Cava near the junction of the hepatic vein.” Further, “injection of 400 ml, followed by a second injection of 400 μl, also showed no significant increase in intravascular pressure.” However, it would be an inherent when an injection volume is increased to 2.5 ml (as in the graph), the pressure in the Inferior Vena Cava near the junction of the hepatic vein or other extravascular cells would increase due to the increased volume of the injection. Furthermore, the increased volume (e.g., from 400 μl to 2.5 ml) would also inherently increase the vascular permeability in the target tissue. Therefore, Twist et al anticipates the claimed invention.

10. Claims 1-2, 4, 6-8, 12-27, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Goddard et al (US Patent # 5602094).

11. The instant claims are drawn to a process for delivering a molecule, and the active steps of the process is inserting an injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue. Claim 30 recites the rapid insertion of a sufficient volume of injection solution.

12. Goddard et al teach the treatment of tumors by administration of PLAP peptide. The reference teaches that two groups of 12 rats were injected with the PLAP and with agarose beads alone (as control). In order to ensure uniform distribution of the bound peptide, the total volumes were increased to 10 ml by the addition of 6 ml sterile saline solution immediately prior to injection. The reference teaches that 72 hours after injection, the rats were euthanized and tumor effusions were aspirated (see column 4, lines 25-45). Since the active steps of the process are disclosed in Goddard patent '094, and the subsequent claims do not alter the active step of the process, Goddard reference meets the limitations of claims 1-2, 4, 6-8, 12-17 and 29-30.

Response to Applicant's Arguments

13. Applicant argues that "Goddard teaches only direct tumor injection of this volume (10 ml). Goddard does not teach "the volume of the injection solution and the rate of injection solution insertion cause transient increased vascular permeability in the target tissue, increased extravascular fluid volume within the target tissue, selling of the target tissue, and extravasation of the molecule via

the increased vascular permeability. Further, Goddard provides no guidance on the volume or rate for intravascular injection."

14. Applicant's arguments have been fully considered but have not been found persuasive because Goddard reference teaches the active step recited in the instant claims. The instant base claim 1 recites the active step "inserting an injection solution containing the proteins or peptide into the lumen of an efferent or afferent vessel of the target tissue." Goddard reference teaches the injection of PLAP protein into the target tissue (tumor). Since a large volume (10 ml) in injected into the target tissue, it would inherently cause an increased vascular permeability, swelling of the target tissue, and increased pressure at the target tissue junction. The instant claims do not recite the volume amount or the rate of injection. Since the active method steps are met by the Goddard reference, the reference anticipates the instant claims.

Obviousness Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

16. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
17. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-2, 4, 6-8, 12-27 and 29-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12, and 14 of U.S. Patent No. 7144869 in view of Rozenberg et al (US 2002/0064520). Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of the instant application, one would necessarily achieve the claimed invention of U.S. Patent '869.

19. The instant claims are drawn to a process for delivering a molecule to an extravascular cell in a mammalian target tissue (liver cell, hepatocyte) in vivo and blood vessel consists of a vein.

20. The claims of U.S. Patent '869 are drawn to a process for delivering a polynucleotide to a primate liver cell, comprising a) transiently occluding afferent and efferent blood vessels of the liver in a primate; and b) injecting the polynucleotide in a solution into the lumen of a hepatic Bessel wherein the injection of the solution results in portal vein pressure of 10 mm Hg or greater (see claims 1-11). Claim 7 recites that the polynucleotide consists of naked DNA (not associated with a transfection reagent or other delivery vehicle). Claims 12 and 14 are further drawn to the hepatic vessel consists of hepatic vein and portal

vein. Assuming about 330 daltons per nucleotide, this implies that for a pair of nucleotide, the molecular weight is 660 daltons. The molecular weight of the DNA would depend on the size of the DNA. The difference between the reference and the instant claims is that the reference does not teach the delivery of protein or peptide to the target tissue.

21. However, Rozenberg et al teach vectors for cell-specific gene delivery to a target cell, and the vectors comprise a recombinant core containing the genetic materials to be delivered (see abstract). The reference further teaches a non-naturally occurring gene therapy vector for cell-specific delivery of nucleic acid to a target cell, wherein at least one expression product of said vector is a therapeutic nucleic acid, peptide or protein (see claim 1). The reference further teaches the method of treating a disease in a patient, comprising administering to said patient a therapeutically effective amount of a vector according to claim 1 (see claim 8).

22. Therefore, it would have been obvious for one of ordinary skill in the art to deliver the protein or peptide directly to the target tissue, since patent '869 teaches the delivery of DNA or RNA into the target tissue, and Rozenberg et al teach the delivery of vectors expressing nucleic acid encoding proteins or peptide to the target tissue of the patient. One of ordinary skill in the art would be motivated to combine the teachings, since the teachings show that both DNA or RNA or nucleic acid encoding the proteins or peptides can be delivered to the target tissue. There is a reasonable expectation of success, since DNA or RNA or nucleic acid encoding the protein or peptide can be delivered to the target

tissue, so one would expect that the proteins or peptides would also be delivered to the target tissue.

23. Claims 1-2, 4, 6-8, 12-17, 29-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 09/000'533 in view of Rozenberg et al (US 2002/0064520).

24. The instant claims are drawn to a process for delivering a molecule to an extravascular cell in a mammalian target tissue (liver cell, hepatocyte) in vivo and blood vessel consists of a vein.

25. The copending Application '533 teaches a process for delivering a polynucleotide (DNA or RNA) to a muscle cell, comprising inserting the polynucleotide into a vessel for delivery to the muscle cell such that the polynucleotide is transfected into the muscle cell. The difference between the reference and the instant claims is that the reference does not teach the delivery of proteins or peptides.

26. However, as described supra, Rozenberg et al teach vectors for cell-specific gene delivery to a target cell, and the vectors comprise a recombinant core containing the genetic materials to be delivered (see abstract). The reference further teaches a non-naturally occurring gene therapy vector for cell-specific delivery of nucleic acid to a target cell, wherein at least one expression product of said vector is a therapeutic nucleic acid, peptide or protein (see claim 1). The reference further teaches the method of treating a disease in a patient,

comprising administering to said patient a therapeutically effective amount of a vector according to claim 1 (see claim 8).

27. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of copending Application No. '533 and Rozenberg et al to deliver the protein or peptide to the target tissue. Copending Application No. '533 teach the delivery of RNA or DNA to muscle cell and Rozenberg et al teach the delivery of DNA or RNA or nucleic acid encoding the protein or peptide to the target tissue of the patient. One of ordinary skill in the art would be motivated to combine the teachings, since the teachings show that both DNA or RNA or nucleic acid encoding the proteins or peptides can be delivered to the target tissue. There is a reasonable expectation of success, since DNA or RNA or nucleic acid encoding the protein or peptide can be delivered to the target tissue, so one would expect that the proteins or peptides would also be delivered to the target tissue.

This is a provisional obviousness-type double patenting rejection.

Conclusion

28. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. H./
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654